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| (54) Title: COSMETIC COMPOSITION CONTAINING CERAMIDE PRECURSORS (57) Abstract A composition for topical application to skin which comprises: (i) from 0.0001 to 10 % by weight of one or more ceramide pathway intermediates or precursors thereof and mixtures thereof; and (ii) a balancing amount of a cosmetically acceptable vehicle for the intermediate. | | |

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COSMETIC COMPOSITION CONTAINING CERAMIDE PRECURSORS

FIELD OF THE INVENTION

5 The invention relates to skin-conditioning compositions and methods. It is particularly concerned with the stimulation of ceramide production in the epidermis, leading to an increase in the level of these lipid materials in the stratum corneum of the skin. The composition is also
10 suitable for topical application to the hair and the nails.

BACKGROUND TO THE INVENTION

15 The stratum corneum, which is the outermost layer of the mammalian skin, contains intercellular lipids consisting predominantly of ceramides, cholesterol and fatty acids. From studies involving lipid depletion of the corneum by solvent extraction and from enzyme inhibition studies, ceramide in particular has been shown to be essential for
20 the barrier function of the stratum corneum.

 In normal skin, if there is perturbation of the barrier function, the epidermis normally re-synthesises the deficient lipids by inducing the expression or activation
25 of the appropriate enzymes. However, under certain conditions, a reduced capacity for re-synthesis of the lipids may occur. This is especially so with elderly subjects, whose stratum corneum ceramide level is in any case reportedly lower than that of younger subjects.

30 The present invention is based upon the concept of stimulating the synthesis of ceramides in the epidermis by the topical application of precursors thereof in the biosynthetic pathway and/or by stimulation of the activity
35 of enzymes responsible for catalysing the steps in the biosynthetic pathway that yields ceramide (as described later in this specification).

Synthesis of Ceramide

5 The synthesis of ceramide in the epidermis can be achieved by a variety of biochemical pathways, for example, those shown in Figure 1.

10 Common to each of these pathways are palmitoyl-CoA and serine, which are converted initially to 3-ketosphinganine in the presence of serine palmitoyl transferase. This is a rate limiting step and can accordingly adversely affect the rate of synthesis of ceramides via 3-ketosphinganine and the other intermediates as shown in these pathways.

15 We have now discovered that the rate of synthesis of ceramide in the epidermis can be increased following topical application of one or more intermediates in these biosynthetic pathways, especially those that are distal to the rate limiting step. We have also discovered that precursors comprising palmitoyl CoA and serine, can
20 together increase ceramide synthesis, even though these are proximal to the rate limiting step.

25 The invention is accordingly concerned with the use of one or more of these ceramide pathway intermediates, following topical application, in enhancing the quality and condition of human skin, especially the water barrier properties thereof, in particular by increasing the rate of ceramide biosynthesis in the epidermis.

30 DEFINITION OF THE INVENTION

According to the invention, there is provided a composition suitable for topical application to human skin which comprises:

35

(i) from 0.0001 to 10% by weight of a ceramide pathway intermediate or a precursor thereof or mixtures thereof;

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and

5 (ii) a balancing amount of a cosmetically acceptable vehicle for the ceramide pathway intermediate or precursor thereof.

10 The invention is also concerned with a method of treating skin, particularly dry and aged skin, with topically applied ceramide pathway intermediate, or a precursor thereof or mixtures thereof, in order to maintain or repair the skin barrier which controls moisture loss from the skin.

15 The invention is also concerned with the use of one or more ceramide pathway intermediates, or precursors thereof or mixtures thereof in maintaining or enhancing the skin barrier function which controls moisture loss from the skin and in the treatment of skin to reduce or delay the development of wrinkles associated with advancing age, or
20 with sun-induced skin ageing.

The invention is also concerned with the use of at least 0.0001% by weight based on the total composition, of a ceramide pathway intermediate in a composition suitable for
25 topical application to human skin comprising a major proportion of a cosmetically acceptable vehicle for the ceramide pathway intermediate.

DISCLOSURE OF THE COMPOSITION OF THE INVENTION

30 The composition according to the invention comprises in its simplest form a ceramide pathway intermediate or a precursor thereof, or mixtures thereof together with a cosmetically acceptable vehicle, the composition being
35 suited for topical application to human skin.

The primary function of the said intermediate or precursor

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thereof is to stimulate the synthesis of ceramide in the epidermis which then leads to higher ceramide levels in the stratum corneum. The water permeability barrier function of the skin, is thereby improved and the ability of the skin to retain moisture consequently enhanced.

The consumer perceived benefits that accordingly accrue from higher levels of ceramide in the stratum corneum achieved in this way are to be seen in the improvement in skin condition, such as eradication or reversal of skin ageing, including removal of age spots, keratoses, wrinkles, skin lines, blotches, blemishes, nodules, pigmented spots, coarse, rough and dry skin, together with improvements in skin barrier function leading to fewer problems of skin sensitivity, photodamaged skin, loss of elasticity and flexibility.

The Ceramide Pathways

With reference to Figure 1, which shows three alternative biosynthetic pathways for the production of ceramides in human skin, it can be seen that each has a common rate limiting step, namely the conversion of palmitoyl-CoA and serine to 3-ketosphinganine in the presence of serine palmitoyltransferase.

With reference to Ceramide Pathway I (Figure 1), 3-ketosphinganine is then converted to sphinganine in the presence of NADPH-dependant reductase and final conversion to Ceramide(A), via sphinganine in the presence of fatty acyl-CoA.

With reference to Ceramide Pathway II, 3-ketosphingosine is converted firstly to sphinganine and then secondly to sphingosine, and then to N-acyl sphingosine (Ceramide (B)).

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With reference to Ceramide Pathway III, 3-ketosphinganine is converted to sphinganine in the presence of NADPH-dependant reductase, as occurs in Ceramide Pathway I, but then sphinganine is converted firstly to sphingosine, and secondly to phytosphingosine and then to N-acylphytosphingosine (Ceramide (C)).

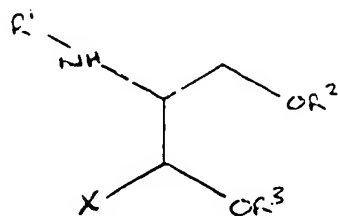
The Ceramides produced via ceramide pathways I, II and III are likely to be structurally different from each other and for this purpose are designated Ceramides (A), (B) and (C).

It is to be understood that the above ceramide pathways are purely illustrative and do not represent the only pathways available for the production of ceramide.

The Ceramide Pathway Intermediates

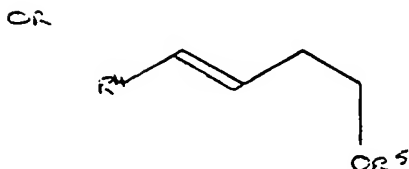
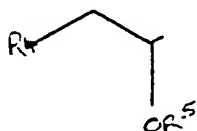
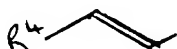
As has been explained, the conversion of palmitoyl-CoA and serine to 3-ketosphinganine in the presence of serine palmitoyltransferase represents the rate limiting step, ie the step which limits the formation of ceramide in the skin and other tissues. Accordingly, in order to enhance the rate at which ceramide is formed, particularly in the skin, it is preferred to deliver to the skin an effective amount of a precursor of ceramide which enters one or more of the Ceramide Pathways distal to this rate limiting step.

The rate of formation of ceramide can thus be enhanced by providing as precursors sphingoid bases, typical examples of which are sphinganine, sphingosine and phytosphingosine and derivatives thereof in accordance with structure (1):

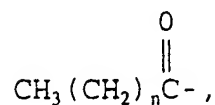
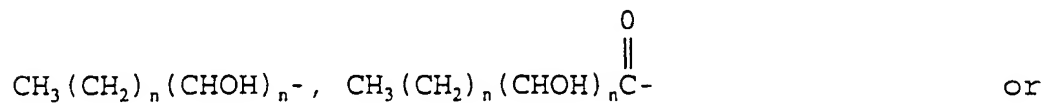


(1)

where X is represented by



and where R^1 , R^2 , R^3 and R^5 are each individually represented by H-, $\text{CH}_3(\text{CH}_2)_n$ -



or phosphorylated, sulphated, glycosylated and benzoyl derivatives thereof;

where n is 0, or an integer of from 1 to 10, and

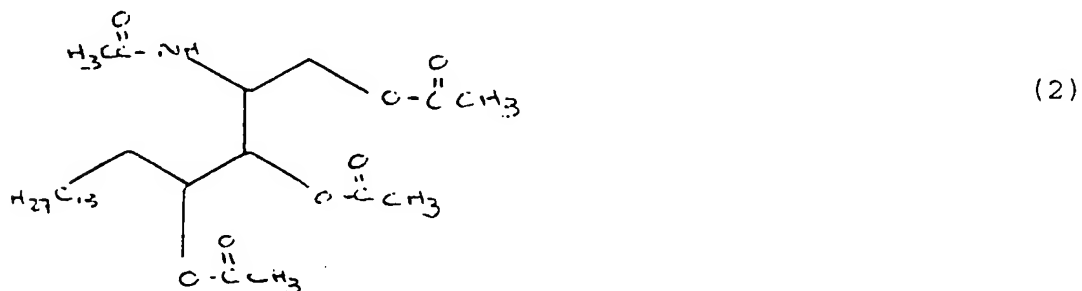
R^4 is $\text{CH}_3(\text{CH}_2)_m$ -

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where m is an integer of from 1 to 21.

One preferred group of ceramide pathway intermediates includes: sphinganine, sphingosine and phytosphingosine and their respective N-acyl, O-acyl and N-alkyl derivatives.

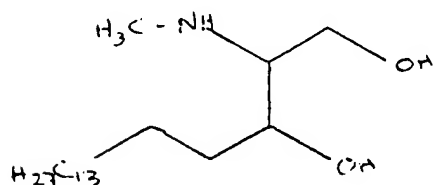
A particularly preferred ceramide pathway intermediate is tetraacetyl phytosphingosine having the structure (2):



Particularly preferred derivatives of sphinganine are N-acetyl sphinganine having the structure (3):



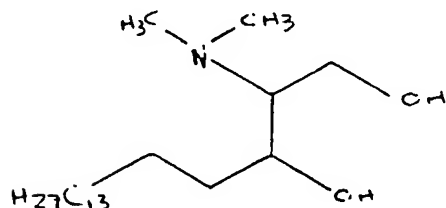
N-methyl sphinganine having the structure (4):



(4)

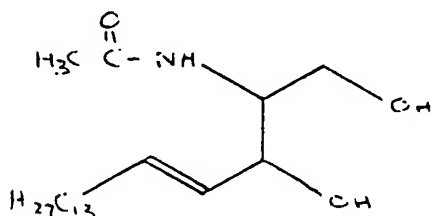
The acyl substituent is suitably a C_{1-16} acyl group preferably acetoxy. Conveniently, the pathway intermediate may be acylated at the N-atom and one or more of the oxygen atom present. The alkyl substituent is suitably C_{1-16} , preferably C_{1-4} , especially methyl. The nitrogen atom may be mono- or di-alkylated.

N,N'-dimethylsphinganine having the structure (5):



(5)

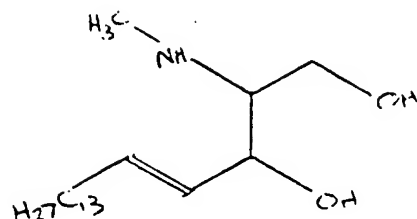
Particular preferred derivatives of sphingosine are -acetylsphingosine having the structure (6):



(6)

N-methyl sphingosine having the structure (7):

5

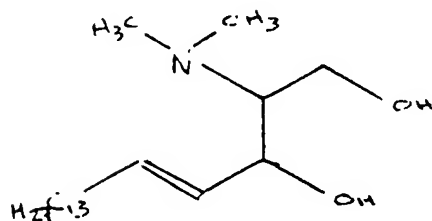


(7)

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N,N'-dimethylsphingosine having the structure (8):

15



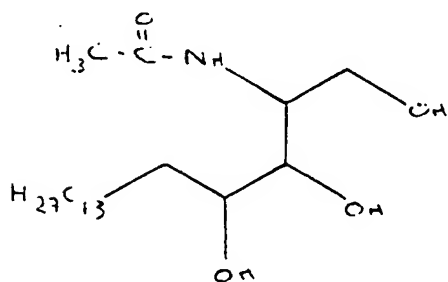
(8)

20

Other particularly preferred derivatives of phytosphingosine are:

N-acetylphytosphingosine having the structure (9):

25



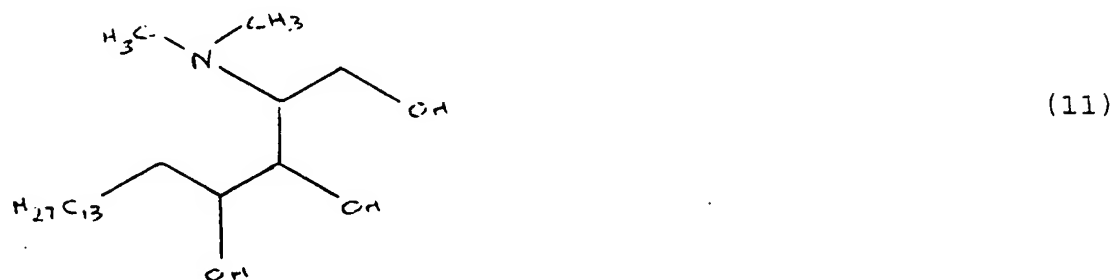
(9)

30

N-methyl phytosphingosine having the structure (10):



10 and N,N' dimethyl phytosphingosine having the structure (11):



20 It is to be understood that the above structures (2) to (11) are illustrative of derivatives of ceramide pathway intermediates which are useful in accordance with the invention and that there are many other derivatives that fit structure (1) that are also useful.

25 As has been explained earlier, it is also possible to employ precursors of ceramide synthesis that occur proximal to the rate limiting step in the ceramide pathway. These precursors are preferably palmitoyl CoA and serine which together are converted to 3-ketosphinganine by the enzyme
30 serine palmitoyltransferase.

35 The amount of a selected ceramide pathway intermediate including precursors thereof or mixture thereof that should be incorporated in the composition according to the invention is from 0.0001 to 10%, preferably from 0.1 to 5% and ideally from 0.05 to 2% by weight of the composition.

THE COSMETICALLY ACCEPTABLE VEHICLE

The composition according to the invention also comprises a solid, semi-solid or liquid cosmetically and/or physiologically acceptable vehicle, to enable the ceramide pathway intermediate to be conveyed to the skin at an appropriate dilution. The nature of the vehicle will depend upon the method chosen for topical administration of the composition. The vehicle can itself be inert or it can possess physiological or pharmaceutical benefits of its own.

The selection of a vehicle for this purpose presents a wide range of possibilities depending on the required product form of the composition. Suitable vehicles can be classified as described hereinafter.

It should be explained that vehicles are substances which can act as diluents, dispersants, or solvents for the ceramide pathway intermediate which therefore ensure that they can be applied to and distributed evenly over the skin, hair or nails at an appropriate concentration. The vehicle is preferably one which can aid penetration of the ceramide pathway intermediate into the skin to enable it more readily to influence the skin condition.

Compositions according to the invention can include water as a vehicle, and/or at least one cosmetically acceptable vehicle other than water.

Vehicles other than water can include liquid or solid emollients, solvents, humectants, thickeners and powders. Examples of each of these types of vehicle, which can be used singly or as mixtures of one or more vehicles, are as follows:

Emollients, such as stearyl alcohol, glyceryl

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monoricinoleate, mink oil, cetyl alcohol, isopropyl isostearate, stearic acid, isobutyl palmitate, isocetyl stearate, oleyl alcohol, isopropyl laurate, hexyl laurate, decyl oleate, octadecan-2-ol, isocetyl alcohol, eicosanyl alcohol, behenyl alcohol, cetyl palmitate, silicone oils
5 such as dimethylpolysiloxane, di-n-butyl sebacate, isopropyl myristate, isopropyl palmitate, isopropyl stearate, butyl stearate, polyethylene glycol, triethylene glycol, lanolin, cocoa butter, corn oil, cotton seed oil,
10 olive oil, palm kernel oil, rapeseed oil, safflower seed oil, evening primrose oil, soybean oil, sunflower seed oil, avocado oil, sesame seed oil, coconut oil, arachis oil, castor oil, acetylated lanolin alcohols, petroleum jelly, mineral oil, squalane, squalene, butyl myristate,
15 isostearic acid, palmitic acid, isopropyl linoleate, lauryl lactate, myristyl lactate, decyl oleate, myristyl myristate;

Propellants, such as propane, butane, isobutane, dimethyl
20 ether, carbon dioxide, nitrous oxide;

Solvents, such as ethyl alcohol, methylene chloride, isopropanol, acetone, ethylene glycol monoethyl ether, diethylene glycol monobutyl ether, diethylene glycol
25 monoethyl ether, dimethyl sulphoxide, dimethyl formamide, tetrahydrofuran;

Powders, such as chalk, talc, fullers earth, kaolin, starch, gums, colloidal silica sodium polyacrylate, tetra
30 alkyl and/or trialkyl aryl ammonium smectites, chemically modified magnesium aluminium silicate, organically modified montmorillonite clay, hydrated aluminium silicate, fumed silica, carboxyvinyl polymer, sodium carboxymethyl cellulose, ethylene glycol monostearate, ethylene glycol
35 distearate;

The cosmetically acceptable vehicle will usually form from

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10 to 99.999%, preferably from 10 to 99% and most preferably from 50 to 99% by weight of the composition, and can, in the absence of other cosmetic adjuncts, form the balance of the composition.

5

Ceramide Pathway Adjuncts

In the biosynthesis of ceramide as hereinbefore described, the provision of ceramide pathway adjuncts in the composition according to the invention is preferable.

10

For example, the ceramide pathway intermediates and precursors thereof are preferably accompanied by saturated or unsaturated, straight or branched chain fatty acids or their esters, particularly their coenzyme A derivatives, or adenosine monophosphate derivatives, or preferably alpha-, beta or omega hydroxylated straight or branched chain fatty acids and esters thereof, especially the omega hydroxy linoleoyl ester.

15

20

The amount of selected ceramide pathway adjuncts, when employed, can be similar to that of the ceramide pathway intermediate or precursor thereof.

25

OPTIONAL SKIN BENEFIT MATERIALS AND COSMETIC ADJUNCTS

Penetration Enhancer

30

The composition according to the invention can also optionally comprise a penetration enhancer which can potentiate the benefit of the ceramide pathway intermediate or precursor thereof by improving its delivery through the stratum corneum to its site of action in the epidermis.

35

The penetration enhancer can accordingly function in a variety of ways. It can for example, improve the distribution of the ceramide pathway intermediate on the

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skin surface or, it can increase its partition into the skin from the composition when applied topically, so aiding its passage to its site of action. Other mechanisms enhancing the benefit of the ceramide pathway intermediate may also be involved.

Examples of penetration enhancers include:

2-methyl propan-2-ol
10 Propan-2-ol
Ethyl-2-hydroxypropanoate
Hexan-2,5-diol
POE(2) ethyl ether
Di(2-hydroxypropyl) ether
15 Pentan-2,4-diol
Acetone
POE(2) methyl ether
2-hydroxypropionic acid
2-hydroxyoctanoic acid
20 Propan-1-ol
1,4 Dioxane
Tetrahydrofuran
Butan-1,4-diol
Propylene glycol dipelargonate
25 Polyoxypropylene 15 stearyl ether
Octyl alcohol
POE ester of oleyl alcohol
Oleyl alcohol
Lauryl alcohol
30 Dioctyl adipate
Dicapryl adipate
Diisopropyl adipate
Diisopropyl sebacate
Dibutyl sebacate
35 Diethyl sebacate
Dimethyl sebacate
Dioctyl sebacate

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Dibutyl suberate
Dioctyl azelate
Dibenzyl sebacate
Dibutyl phthalate
5 Dibutyl azelate
Ethyl myristate
Dimethyl azelate
Butyl myristate
Dibutyl succinate
10 Didecyl phthalate
Decyl oleate
Ethyl caproate
Ethyl salicylate
Isopropyl palmitate
15 Ethyl laurate
2-ethyl-hexyl pelargonate
Isopropyl isostearate
Butyl laurate
Benzyl benzoate
20 Butyl benzoate
Hexyl laurate
Ethyl caprate
Ethyl caprylate
Butyl stearate
25 Benzyl salicylate
Dimethyl sulphoxide
N,N-Dimethyl acetamide
N,N-Dimethyl formamide
2-Pyrrolidone
30 1-Methyl-2-pyrrolidone
5-Methyl-2-pyrrolidone
1,5-Dimethyl-2-pyrrolidone
1-Ethyl-2-pyrrolidone
Phosphine oxides
35 Sugar esters
Tetrahydrofurfural alcohol
Urea

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Diethyl-m-toluamide, and
1-Dodecylazacycloheptan-2-one

5 The amount of penetration enhancer, when employed in accordance with the invention, will normally be from 0.1 to 50%, preferably from 0.5 to 25% and most preferably from 0.5 to 10% by weight of the composition.

10 A particularly convenient form of the composition according to the invention is an emulsion, in which case an oil or oily material will normally be present, together with an emulsifier to provide either a water-in-oil emulsion or an oil-in-water emulsion, depending largely on the average hydrophillic-lyophilic balance (HLB) of the emulsifier
15 employed.

Oil or Oily Material

20 The composition according to the invention can optionally comprise one or more oils or other materials having the properties of an oil.

Examples of suitable oils include mineral oil and vegetable oils, and oil materials, such as those already proposed
25 herein as emollients. Other oils or oily materials include silicone oils, both volatile and non-volatile, such as polydimethyl siloxanes.

30 The oil or oily material, when present for the purposes for forming an emulsion, will normally form up to 90%, preferably from 10 to 80% by volume of the composition.

Emulsifier

35 The composition according to the invention can also optionally comprise one or more emulsifiers the choice of which will normally determine whether a water-in-oil or

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and oil-in-water emulsion is formed.

When a water-in-oil emulsion is required, the chosen emulsifier or emulsifiers should normally have an average HLB value of from 1 to 6. When an oil-in-water emulsion is required, a chosen emulsifier or emulsifiers should have an average HLB value of >6 .

Examples of suitable emulsifiers are set below in Table 1 in which the chemical name of the emulsifiers is given together with an example of a trade name as commercially available, and the average HLB value.

TABLE 1

15

| ----- | | |
|-------|---|---------------------------------|
| | Chemical Name of Emulsifier | Trade Name HLB Value |
| ----- | | |
| 20 | Sorbitan trioleate | Arlacel 85 1.8 |
| | Sorbitan tristearate | Span 65 2.1 |
| | Glycerol monooleate | Aldo MD 2.7 |
| | Glycerol monostearate | Atmul 84S 2.8 |
| | Glycerol monolaurate | Aldo MC 3.3 |
| 25 | Sorbitan sesquioleate | Arlacel 83 3.7 |
| | Sorbitan monooleate | Arlacel 80 4.3 |
| | Sorbitan monostearate | Span 60 4.7 |
| | Poloxyethylene (2) stearyl ether | Brij 72 4.9 |
| 30 | Poloxyethylene sorbitol beeswax derivative | G-1702 5 |
| | PEG 200 dilaurate | Emerest 2622 6.3 |
| | Sorbitan monopalmitate | Arlacel 40 6.7 |
| | Polyoxyethylene (3.5) nonyl phenol | Emulgen 903 7.8 |
| 35 | PEG 200 monostearate | Tegester PEG 200 MS 8.5 |

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| | | | |
|----|--|------------------------|------|
| | Sorbitan monolaurate | Arlacel 200 | 8.6 |
| | PEG 400 dioleate | Tegester PEG 400-DO | 8.8 |
| | Polyoxyethylene (5) | | |
| 5 | monostearate | Ethofat 60-16 | 9.0 |
| | Polyoxyethylene (4) sorbitan monostearate | Tween 61 | 9.6 |
| | Polyoxyethylene (4) lauryl ether | Brij 30 | 9.7 |
| 10 | Polyoxyethylene (5) sorbitan monooleate | Tween 81 | 10.0 |
| | PEG 300 monooleate | Neutronyx 834 | 10.4 |
| | Polyoxyethylene (20) sorbitan tristearate | Tween 65 | 10.5 |
| 15 | Polyoxyethylene (20) sorbitan trioleate | Tween 85 | 11.0 |
| | Polyoxyethylene (8) monostearate | Myrj 45 | 11.1 |
| | PEG 400 monooleate | Emerest 2646 | 11.7 |
| 20 | PEG 400 monostearate | Tegester PEG 400 | 11.9 |
| | Polyoxyethylene 10 monooleate | Ethofat 0/20 | 12.2 |
| | Polyoxyethylene (10) stearyl ether | Brij 76 | 12.4 |
| 25 | Polyoxyethylene (10) cetyl ether | Brij 56 | 12.9 |
| | Polyoxyethylene (9.3) octyl phenol | Triton X-100 | 13.0 |
| | Polyoxyethylene (4) sorbitan monolaurate | Tween 21 | 13.3 |
| 30 | PEG 600 monooleate | Emerest 2660 | 13.7 |
| | PEG 1000 dilaurate | Kessco | 13.9 |
| | Polyoxyethylene sorbitol lanolin derivative | G-1441 | 14.0 |
| 35 | Polyoxyethylene (12) lauryl ether | Ethospense LA-12 | 14.4 |
| | PEG 1500 dioleate | Pegospense 1500 | 14.6 |

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| | | | |
|----|-----------------------------|-----------------|------|
| | Polyoxyethylene (14) | | |
| | laurate | Arosurf HFL-714 | 14.8 |
| | Polyoxyethylene (20) | | |
| | sorbitan monostearate | Tween 60 | 14.9 |
| 5 | Polyoxyethylene 20 sorbitan | | |
| | monooleate | Tween 80 | 15.0 |
| | Polyoxyethylene (20) | | |
| | stearate | Myrj 49 | 15.0 |
| | Polyoxyethylene (20) | | |
| 10 | stearyl ether | Brij 78 | 15.3 |
| | Polyoxyethylene (20) | | |
| | sorbitan monopalmitate | Tween 40 | 15.6 |
| | Polyoxyethylene (20) cetyl | | |
| | ether | Brij 58 | 15.7 |
| 15 | Polyoxyethylene (25) | | |
| | oxypropylene | | |
| | monostearate | G-2162 | 16.0 |
| | Polyoxyethylene (20) | | |
| | sorbitol monolaurate | Tween 20 | 16.7 |
| 20 | Polyoxyethylene (23) | | |
| | lauryl ether | Brij 35 | 16.9 |
| | Polyoxyethylene (50) | | |
| | monostearate | Myrj 53 | 17.9 |
| | PEG 4000 monostearate | Pegosperse 4000 | |
| 25 | | MS | 18.7 |

30 The foregoing list of emulsifiers is not intended to be limiting and merely exemplifies selected emulsifiers which are suitable for use in accordance with the invention.

It is to be understood that two or more emulsifiers can be employed if desired.

35

The amount of emulsifier or mixtures thereof, to be incorporated in the composition of the invention, when

- 20 -

appropriate is from 1 to 50%, preferably from 2 to 20% and most preferably from 2 to 10% by weight of the composition.

Silicone Surfactant

5

The composition of the invention can also optionally comprise a high molecular weight silicone surfactant which can also act as an emulsifier, in place of or in addition to the optional emulsifier(s) already mentioned.

10

The silicone surfactant is a high molecular weight polymer of dimethyl polysiloxane with polyoxyethylene and/or polyoxypropylene side chains having a molecular weight from 10,000 to 50,000.

15

The dimethyl polysiloxane polymer is conveniently provided as a dispersion in a volatile siloxane, the dispersion comprising, for example, from 1 to 20% by volume of the polymer and from 80 to 99% by volume of the volatile siloxane. Ideally, the dispersion consists of a 10% by volume of the polymer dispersed in the volatile siloxane.

20

Examples of the volatile siloxanes in which the polysiloxane polymer can be dispersed include polydimethyl siloxane (pentamer and/or hexamer).

25

A particularly preferred silicone surfactant is cyclomethicone and dimethicone copolyol, such as DC 3225C Formulation Aid available from DOW CORNING. Another is laurylmethicone copolyol, such as DC Q2-5200, also available from Dow Corning.

30

The amount of silicone surfactant, when present in the composition will normally be up to 25%, preferably from 0.5 to 15% by weight of the emulsion.

35

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Retinoids

The composition according to the invention optionally can also comprise a retinoid, such as retinoic acid or retinol (Vitamin A) and/or derivative thereof, further to enhance the benefits to skin of the ceramide pathway intermediate.

In addition to retinol itself, examples of derivatives of retinol include:

Retinyl acetate
Retinyl butyrate
Retinyl propionate
Retinyl octanoate
Retinyl laurate
Retinyl palmitate
Retinyl oleate
Retinyl linoleate, and
Retinyl linolenate.

The amount of retinoid, when present in the composition according to the invention is from 0.01 to 10% and preferably 0.1 to 5% by weight of the composition.

Tocopherol

The composition according to the invention optionally can also comprise a tocopherol (vitamin E group), as an antioxidant for the retinoid, when present in the composition, and to limit oxidative damage to skin. The vitamin E group comprises α -tocopherol, β -tocopherol, γ -tocopherol and δ -tocopherol.

The amount of a tocopherol, when present in the composition according to the invention, is from 0.0001 to 20%, preferably from 0.0001 to 10% by weight of the composition.

Water

The composition of the invention can also comprise water, usually up to 90%, preferably from 5 to 80% by volume.
5 Water can function as the cosmetically acceptable vehicle.

OTHER COSMETIC ADJUNCTS

10 Examples of other cosmetic adjuncts which can optionally be employed in the composition according to the invention include preservatives, such as para-hydroxy benzoate esters; antioxidants, such as butyl hydroxy toluene; humectants, such as glycerol, sorbitol, 2-pyrrolidone-5-carboxylate, dibutylphthalate, gelatin, polyethylene,
15 glycol, preferably PEG 200-600; buffers, such as lactic acid together with a base such as triethanolamine or sodium hydroxide; surfactants, such as glycerol ethers; ceramides of synthetic, animal or plant origin; pseudoceramides; phospholipids; vitamins, such as 1,25 dihydroxy
20 cholecalciferol; waxes, such as beeswax, ozokerite wax, paraffin wax, plant extracts, such as Aloe vera, cornflower, witch hazel, elderflower, cucumber, thickeners; activity enhancers; colourants; perfumes; and sunscreen materials such as ultrafine titanium dioxide and organic
25 sunscreens such as p-aminobenzoic acid and esters thereof, ethylhexyl p-methoxycinnamate, 2-ethoxyethyl p-methoxycinnamate and butyl methoxydibenzoylmethane, and mixtures thereof.

30 In a further preferred composition, the ceramide pathway intermediate is combined with ceramides, pseudoceramides, polyol fatty acid polyesters, sterols, particularly cholesterol, galactosyldiacyl-glycerols, glycosphingolipids, fatty acids and esters thereof and
35 mixtures thereof and other ingredients, such as mevalonic acid, hexadecylsuccinic acid monobehenyl ester ethoxylate (7.3 EO) and/or derivatives thereof to produce a liposomal

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dispersion. Preferred ceramide pathway adjuncts include ceramides, cholesterol, cholesterol pathway intermediates or precursors thereof such as mevalonic acid and fatty acid pathway intermediates or precursors thereof such as acetic acid and malonic acid.

A further preferred composition may also contain in combination with the ceramide pathway intermediate and optional additional ingredients disclosed above, an organic acid component chosen from hydroxy carboxylic acids, such as alpha, beta and omega hydroxyacids, especially glycolic acid, lactic acid and 2-hydroxyoctanoic acid, and keto carboxylic acids, esters thereof and mixtures thereof. It will be appreciated that the invention includes within its scope all enantiomers, diastereomers and mixtures thereof.

In yet another preferred composition, the ceramide pathway intermediate is dissolved in squalene or squalane, optionally together with ceramides and other ingredients, such as mevalonic acid and malonic acid and/or derivatives thereof and formulated with volatile and non-volatile silicones to produce an anhydrous or nearly anhydrous single phase system.

Cosmetic adjuncts can form the balance of the composition.

PRESERVATION OF THE COMPOSITION

The composition according to the invention is preferably preserved in such a manner that it will enjoy an extended shelf life following manufacture and prior to sale and use. Ideally the composition will have an indefinite shelf life.

It is accordingly apparent that the ceramide pathway intermediate is likely to be prone to attack by bacteria, moulds and fungi and other microbial influences, particularly at pH values near that of the skin that characterise the preferred composition. The shelf-life of

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the composition can therefore be unacceptably short due to the biodegradation of the precursor unless steps are taken to preserve the composition.

5 In order to be preserved, the composition should preferably be free, or substantially free, from viable microbial contaminants that are capable of resulting in microbial spoilage of the composition, and/or biodegradation of the precursor prior to topical application of the composition
10 to mammalian skin or hair. It is to be understood, however, that the invention is also concerned with compositions, as herein defined, which may contain viable but dormant microorganisms, such as bacterial spores, provided that the conditions of preservation do not result
15 in substantial proliferation of the microorganisms prior to use of the composition.

Examples of the methods that can be employed to achieve preservation of the composition, includes the following:

20

(i) Sterilisation

The composition according to the invention can be preserved by sterilisation to remove or kill substantially all viable
25 microbial contaminants. This can be achieved for example by irradiation using a lethal dose of gamma rays, by heat sterilisation or by ultrafiltration using techniques that are well established in the pharmaceutical industry.

30

(ii) Chemical Preservative

The composition according to the invention can also be preserved by including in it a chemical preservative which functions to prevent the growth of or kill bacteria, fungi
35 or other microorganisms.

Examples of chemical preservatives include ethanol, benzoic

- 25 -

acid, sodium benzoate, sorbic acid, potassium sorbate, sodium propionate and the methyl, ethyl, propyl and butyl esters of p-hydroxybenzoic acid. The amount of chemical preservative that can be incorporated in the composition according to the invention will generally be from 0.05 to 5%, preferably from 0.1 to 2% by weight, the amount chosen being sufficient to arrest microbial proliferation.

(iii) Water activity depressants

10

The composition according to the invention can also be preserved by the inclusion of a water activity depressant such as glycerol, propylene glycol, sorbitol, sugars and salts, for examples alkali metal halides sulphates and carboxylates. When employing a water activity depressant, sufficient should be incorporated in the composition according to the invention to reduce the water activity (α_w) from 1 to < 0.9 , preferably to < 0.85 and most preferably < 0.8 , the lowest of these values being that at which yeasts, moulds and fungi will not proliferate.

20

PROCESS

The invention also provides a process for preparing a composition according to the invention which comprises the steps of mixing an effective amount of a ceramide pathway intermediate, as herein defined, together with a cosmetically acceptable carrier for the intermediate.

25

USE OF THE COMPOSITION

30

The composition according to the invention is intended primarily as a product for topical application to human skin, for maintaining or enhancing the skin barrier function, particularly by stimulating the synthesis of ceramides. The composition is particularly useful for treating dry, ageing or damaged skin to reduce moisture

35

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loss, increase stratum corneum flexibility and to enhance the quality of skin. The composition can also be applied to the hair or nails.

5 In use, a small quantity of the composition, for example from 1 to 5ml, is applied to exposed areas of the skin, hair or nails, from a suitable container or applicator and, if necessary, it is then spread over and/or rubbed into the area to be treated using the hand or fingers or a suitable
10 device.

PRODUCT FORM AND PACKAGING

The topical skin and/or hair and/or nail treatment
15 composition of the invention can be formulated as a lotion having a viscosity of from 4,000 to 10,000 mPas, a fluid cream having a viscosity of from 10,000 to 20,000 mPas or a cream having a viscosity of from 20,000 to 100,000 mPas, or above. The composition can be packaged in a suitable
20 container to suit its viscosity and intended use by the consumer.

For example, a lotion or fluid cream can be packaged in a bottle or a roll-ball applicator or a propellant-driven
25 aerosol device or a container fitted with a pump suitable for finger operation. When the composition is a cream, it can simply be stored in a non-deformable bottle or squeeze container, such as a tube or a lidded jar.

30 The invention accordingly also provides a closed container containing a cosmetically acceptable composition as herein defined.

EVIDENCE OF EPIDERMAL LIPID (CERAMIDE) BIOSYNTHESIS

35 The biosynthesis of epidermal lipid, especially ceramides, can be determined by the method described below.

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Results of ceramide biosynthesis from sphingosine as the ceramide pathway intermediate are also given.

In-vitro measurement of epidermal lipid biosynthesis

5

10

The stimulatory effect of ceramide pathway intermediates (CPI) on lipid levels in the epidermis can be quantified by in-vitro measurements of the level of incorporation of radiolabelled lipid precursors into epidermal lipids over relatively short periods of time (24 hours).

1. Method

15

20

25

30

Punch biopsies (6mm) were taken of full thickness skin scraped free of subcutaneous fat, and floated dermis side downwards onto 3ml of culture medium (MCDB 153 without animal sera, growth factors, or hormones ex Sigma Chemical Co.), containing radiolabelled lipid precursor ($4\mu\text{Ci/ml}$ of 1- ^{14}C acetic acid, sodium salt, 7.4 MBq/ml ex Amersham) and CPI (in 96% v/v ethanol vehicle). Following a 24 hour incubation at 37°C in air (Harvard/LTE incubator), epidermis was isolated from the dermis by incubation in 10mM ethylenediaminetetraacetic acid solution at 37°C for 30 minutes, and placed into 3ml of chloroform:methanol (2:1 v/v) solution for lipid extraction. After 18 hours 0.75ml of potassium chloride solution (0.88% w/v) was added with mixing which after centrifugation produced 2 liquid phases, an upper aqueous phase, and a lower organic phase containing the lipids. Beckman ReadySafe scintillation fluid (4ml) was added to $100\mu\text{l}$ aliquots of the organic phase and counted in a Beckman LS 6000IC scintillation counter to determine the radioactivity present in the lipids.

35

Subsequently 1ml aliquots of the organic phase were evaporated to dryness under nitrogen, redissolved in $100\mu\text{l}$ of chloroform:methanol (2:1 v/v), and transferred to a high

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performance thin layer chromatography plate (HPTLC, silica gel 60, 10x20 cm ex Merck). To resolve the various lipid classes, the plate was run successively with i) chloroform:methanol:acetone (76:20:4) to 15 and then 30mm, ii) chloroform:methanol:acetone (79:12.5:8.5) to 80mm, and finally iii) chloroform:ethyl acetate:diethyl ether:methanol (72:20:6:2) to 95mm. After drying at 120C the plate was saturated with 15ml of acidic copper sulphate solution (10% copper sulphate, 8% phosphoric acid) for 1 minute and then the lipids charred by heating to 120C for 1 minute and then 160C for 10 minutes. Lipid bands were identified using authentic lipid standards (Sigma Chemical Co.) and were quantified by reflectance densitometric scanning at 420nm using a Shimadzu CS-9000 flying spot densitometer. Plates were then placed onto X-ray film (Amersham Multipurpose MP) in cassettes with intensifying screens and exposed for 1 to 4 weeks. Films were developed with a Fuji RGII X-ray film processor and bands quantified by transmission densitometric scanning at 530nm using a Shimadzu CS-9000 flying spot densitometer.

Specific activity was calculated by dividing the radioactivity in each band by the mass of lipid in each band. Each lipid class was identified using authentic lipid standards.

2. Statistical Analysis

Mean values were compared using Students t test and significance was set at the 5% level.

3. Results

The effect of the CPI, sphingosine, on epidermal lipid biosynthesis on three separate occasions: (Experiments A, B & C), is shown in Figure 2. An increase in the level of radiolabelled acetate incorporated into epidermal lipids

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was evident when sphingosine (SPH) was present in the medium at a level of 0.08mM, producing a consistent 20-25% increase over control (C, incubated without sphingosine) after 24 hours, indicating a reproducible stimulation of epidermal lipid biosynthesis.

The effect of sphingosine on individual lipid classes was determined using HPTLC. For each lipid class examined sphingosine at 0.08mM increased the level of incorporation of radiolabelled acetate in comparison to the control (no sphingosine). The specific activity (radioactivity/lipid mass) for each lipid class and the ratio of sphingosine treated to control is shown in Table 1. The ceramide and glucosylceramide class showed the greatest increase in radioactivity incorporation following sphingosine treatment followed by non-polar lipids and finally phospholipids and cholesterol sulphate.

Table 1 : Effect of sphingosine on the specific activity of various lipid classes

| Lipid | Specific Activity (radio activity/mass) | | |
|------------------|---|---------------|-------------|
| | Control | Sphingosine | Ratio SPH/C |
| Non-polar | 0.031 (0.017) | 0.066 (0.059) | 2.13 |
| Ceramide | 0.0085 (0.0044) | 0.029 (0.028) | 3.40 |
| Glucosylceramide | 0.045 (0.024) | 0.136 (0.140) | 3.02 |
| Chol. sulphate | 0.297 (0.0762) | 0.424 (0.150) | 1.43 |
| Phospholipid | 0.264 (0.105) | 0.412 (0.193) | 1.56 |

Data shown as Mean (standard deviation), n=4 for control and sphingosine treated.

4. Conclusions

Sphingosine stimulates epidermal lipid biosynthesis,

- 30 -

increasing the synthesis of all the lipid classes examined, but particularly the glucosylceramide and ceramide class.

Effect of ceramide precursors on keratinocyte
glucosylceramide synthesis

1. Method

Human keratinocytes (ex clonetics) were seeded in 6 well plates and allowed to reach 80% confluency after incubation in Keratinocyte Growth Medium (KGM ex clonetics, 0.15mM calcium) at 37C, 5% CO₂. Fresh medium was added containing radiolabelled lipid precursor (2 μ Ci/ml of 1-¹⁴C acetic acid, sodium salt, 7.4 MBq/ml ex Amersham) and CPI (in 96% v/v ethanol vehicle) and incubated for 24 hours as above. Cells were harvested by scraping, lyophilized, and lipids extracted using 3ml of chloroform:methanol solution (2:1 v/v) as above. Scintiverse BD scintillation fluid (10ml ex Fisher) was added to 100 μ l aliquots of the organic phase and counted in a Beckman LS 6000 IC Scintillation counter to determine the radioactivity present in the lipids.

Subsequently, 200 μ l aliquots of the organic phase were applied to 1cc aminopropyl-silica columns (ex Walters) and lipid fractions eluted by successive washes of hexane, chloroform:isopropanol (2:1 v/v), and acetic acid (2% v/v) in methanol. Radioactivity in each fraction was determined as above and compared to the total radioactivity of all the lipids. Furthermore fractions were evaporated to dryness, redissolved in 20 μ l of chloroform:isopropanol (2:1 v/v) and lipid species present in each fraction identified by high performance thin layer chromatography as described in HPTLC for the organ culture experiments.

2. Statistical analysis

Mean values were compared using students t test and

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significance was set at the 5% level.

3. Results

5 The effects of the CPI's sphingosine (SPH),
phytosphingosine (PHYT), and tetraacetylphytosphingosine
(TAPS) on glucosylceramide synthesis (as identified by
HPTLC) is shown in Figure 3. A significant increase above
control (no CPI present) over 24 hours in the proportion of
10 radiolabelled acetate incorporated into all lipid was
evident when CPI was present in the medium as a level of
0.02mM, indicating a stimulation of keratinocyte
glucosylceramide synthesis. Furthermore, TAPS produced a
significantly higher proportion of radiolabel incorporated
15 that SPH (Figure 3) indicating that TAPS stimulates the
synthesis of glucosylceramide more than SPH. PHYT was more
effective than SPH, but less effective than TAPS.

20 Incorporation of Lipid Precursors into Ceramides/Cerebrosides in Keratinocytes in culture

METHOD

Cell Culture:

25 Human Keratinocytes were grown to 90% confluency in serum-
free Keratinocyte Growth Medium (KGM, Clonetics
Corporation, San Diego CA) containing 0.15mM calcium.
Cells were incubated with lipid precursors
30 (phytosphingosine, tetraacetylphytosphingosine and
juniperic acid) dissolved in ethanol for 24h. Following
incubation the cells were harvested in 1.8mL of potassium
chloride solution (0.88% w/v), the lipids extracted using
chloroform:methanol, and the chloroform layer containing
35 the lipids was analysed by high performance thin layer
chromatography.

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Lipid Analysis:

The organic phase was dried under nitrogen, and resuspended in 200 μ L of chloroform. Different lipid classes were separated based upon their polarity, using aminopropyl column chromatography. 200 μ L of lipid was eluted with successive washes of hexane, hexane:ethyl acetate (85:15 v/v), and chloroform:isopropanol (2:1 v/v). The fractions were then evaporated to dryness under nitrogen, and resuspended in 100 μ L of chloroform:methanol (2:1 v/v). 1/3 of the lipid was spotted onto high performance thin layer chromatography (HPTLC) silica gel plates and developed with an appropriate solvent system. Following lipid separation, the plate was dipped in a 10% copper sulphate solution, charred at 165°C for 20 minutes, and quantified via reflectance densitometry.

Results:

Tetra-acetyl phytosphingosine (TAPS) and phytosphingosine (PHYT) and juniperic acid (HA) were examined for their potential to generate phytoceramide 1, a ceramide 1-like molecule. Due to the extra hydroxyl group present on TAPS and PHYT compared with sphingosine the ceramide generated chromatographically migrates between ceramide 1 and 2. As can be seen from the results TAPS and HA produce significant amounts of phytoceramide 1. PHYT and HA, however, produce more of the glucosyl derivatives.

Conclusions:

The combination of a sphingoid-base and an omega hydroxy fatty acid is capable of being used by keratinocytes to generate a ceramide 1-like molecule.

Effect of Ceramide I Precursors on Phytoceramide I Levels

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| | | Phytoceramide I as % of total lipid | Standard Deviation |
|---|---------|--|-----------------------|
| 1 | Control | 0.881 | 0.048 |
| 2 | HA | 0.816 | 0.125 |
| 3 | PHYT | 0.659 ** | 0.113 |
| 4 | HA+PHYT | 0.357 * | 0.070 |
| 5 | TAPS | 1.310 ** | 0.204 |
| 6 | HA+TAPS | 3.896 ** | 0.863 |

* P < 0.1

** P < 0.5

| | | Glucosylceramide I as % of total lipid | Standard Deviation |
|---|---------|---|-----------------------|
| 1 | Control | 1.340 | 0.527 |
| 2 | HA | 1.526 | 0.284 |
| 3 | PHYT | 4.217 * | 1.000 |
| 4 | HA+PHYT | 5.417 * | 0.900 |
| 5 | TAPS | 4.424 * | 0.535 |
| 6 | HA+TAPS | 1.577 | 0.493 |

* P ≤ 0.05

CLINICAL STUDIES1. Stratum corneum ceramide levels following topical TAPS treatment

In a one-month clinical study on 10 subjects, a 1% solution of tetraacetylphytosphingosine (TAPS) in an

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ethanol/propylene glycol (1:1) vehicle was applied to the volar forearm twice daily; an adjacent site on the forearm was treated with vehicle alone. The dosage amount was 100 μ l applied to approximately 35 sq cm. After one month of treatment, a skin surface biopsy was taken from each site by tape-stripping with sellotape polyester tape. Each 'biopsy' consisted of eight consecutive tape strips of 2x3 cm each. Stratum corneum material was released from the tape by sonication in methanol, the methanol was dried off, and lipids were extracted in 2:1 chloroform:methanol. Solid phase extraction columns were used for preliminary lipid separation, followed by high performance thin layer chromatography (HPTLC) and densitometry for ceramide quantitation. The delipidized squames were incubated in protein extraction buffer, and protein content was determined by Pierce BCA assay.

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| ng Ceramide/ μ g Protein | | | |
|------------------------------|-----------------|--------------|--------|
| Subject | Vehicle-treated | TAPS-treated | Change |
| 1 | 34.42 | 45.21 | + |
| 2 | 36.22 | 42.09 | - |
| 3 | 59.16 | 90.61 | + |
| 4 | 44.27 | 48.02 | + |
| 5 | 25.96 | 43.31 | + |
| 6 | 44.10 | 52.51 | + |
| 7 | 52.66 | 59.85 | + |
| 8 | 80.26 | 42.20 | - |
| 9 | 75.81 | 56.43 | + |
| 10 | 40.56 | 27.82 | - |
| Mean | 49.3 | 50.8 | |
| S.D. | 17.8 | 16.6 | |

Paired t-test: Means not significantly different

Subjects showing increased ceramide levels following TAPS treatment (N=7):

| Treatment | ng Lipid/ μ g Protein | | |
|---------------|---------------------------|-------------|-------------|
| | Ceramide | Cholesterol | Fatty Acid |
| TAPS | 54.5 (17.1) | 24.2 (10.1) | 75.0 (49.1) |
| Vehicle | 42.4 (11.3) | 18.5 (4.4) | 55.7 (21.1) |
| Paired t-test | p=0.015 | n.s.d. | n.s.d. |

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Conclusions

These results show that TAPS improves the levels of ceramides in the stratum corneum but has no effect on cholesterol and fatty acid levels, indicating its specificity as a ceramide precursor.

EXAMPLES

The invention is illustrated by the following examples.

Example 1

This example illustrates a high internal phase water-in-oil emulsion.

A high internal phase water-in-oil emulsion having the following formulation was prepared:

| | <u>% w/w</u> |
|--------------------------------------|--------------|
| Fully hydrogenated coconut oil | 3.9 |
| phytosphingosine | 0.1 |
| Brij 92* | 5 |
| Bentone 38 | 0.5 |
| Preservative | 0.3 |
| MgSO ₄ ·7H ₂ O | 0.3 |
| Butylated hydroxy toluene | 0.01 |
| Perfume | qs |
| Water | to 100 |

*Brij 92 is polyoxyethylene (2) oleyl ether

Example 2

This example also illustrates a high internal phase water-in-oil emulsion in which the formulation of Example 1 was prepared but with the following changes:

- 37 -

- i. liquid paraffin replaced the fully hydrogenated coconut oil, and
- ii. partially esterified phytosphingosine having the structure (11), replaced phytosphingosine per se.

Example 3

This example also illustrates a high internal phase water-in-oil emulsion in which the formulation of Example 1 was prepared, except that sphingosine replaced phytosphingosine per se.

Example 4

This example illustrates an oil-in-water cream.

An oil-in-water cream emulsion having the following formulation was prepared:

| | <u>% w/w</u> |
|---|--------------|
| Mineral oil | 4 |
| Sphingosine derivative having the structure (8) | 0.1 |
| Brij 56* | 4 |
| Alfol 16RD* | 4 |
| Triethanolamine | 0.75 |
| Butane-1,3-diol | 3 |
| Xanthan gum | 0.3 |
| Preservative | 0.4 |
| Perfume | qs |
| Butylated hydroxy toluene | 0.01 |
| Water | to 100 |

*Brij 56 is cetyl alcohol POE (10)
Alfol 16RD is cetyl alcohol

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Example 5

This example also illustrates an oil-in-water emulsion, in which the formulation of example 4 was prepared, except that the sphinganine derivative having the structure (5) replaced the sphingosine derivative having the structure (8).

Example 6

This example also illustrates an oil-in-water emulsion in which the formulation of example 4 was prepared, except that sphinganine replaced the sphingosine derivative having the structure (8).

Example 7

This example illustrates an alcoholic lotion according to the invention.

The lotion had the following formulation:

| | <u>% w/w</u> |
|-----------------------------|--------------|
| Phytosphingosine derivative | |
| having the structure (10) | 0.2 |
| Ethanol | 40 |
| Perfume | qs |
| Butylated hydroxy toluene | 0.01 |
| Water | to 100 |

Example 8

This example illustrates an alcoholic lotion containing a sphingosine derivative of the invention.

The lotion had the following formulations:

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| | | <u>% w/w</u> |
|---|--------------------------|--------------|
| | Sphingosine derivative | |
| | having the structure (6) | 0.2 |
| | Dimethylsulphoxide | 10 |
| 5 | Ethanol | 40 |
| | Antioxidant | 0.1 |
| | Perfume | qs |
| | Water | to 100 |

10 Examples 9 and 10

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

15

| | | <u>% w/w</u> | |
|----|--------------------------------|--------------|-----------|
| | | <u>9</u> | <u>10</u> |
| | phytosphingosine | 1.5 | - |
| | Sphingosine | | 0.5 |
| 20 | having the structure (7) | | |
| | Perfume | 0.1 | 0.1 |
| | Hydroxyethyl cellulose | 0.4 | 0.4 |
| | Absolute ethanol | 25 | 25 |
| | p-methyl benzoate | 0.2 | 0.2 |
| 25 | Sterilised demineralised water | to 100 | to 100 |

Examples 11 and 12

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

30

- 40 -

| | | <u>% w/w</u> | |
|---|--|--------------|-----------|
| | | <u>11</u> | <u>12</u> |
| | sphinganine derivative having the structure (4) | 0.08 | - |
| 5 | sphinganine | - | 0.15 |
| | Ethanol | 10 | 10 |
| | Perfume | 0.5 | 0.5 |
| | Distilled water | to 100 | to 100 |

10 Example 13

This example illustrates a high internal phase water-in-oil emulsion.

15 A high internal phase water-in-oil emulsion having the following formulation was prepared:

| | | <u>% w/w</u> |
|----|--|--------------|
| | Fully hydrogenated coconut oil | 3.9 |
| 20 | tetraacetyl phytosphingosine (Structure 2) | 0.1 |
| | Brij 92* | 5 |
| | Bentone 38 | 0.5 |
| | Preservative | 0.3 |
| | MgSO ₄ ·7H ₂ O | 0.3 |
| 25 | Butylated hydroxy toluene | 0.01 |
| | Perfume | qs |
| | Water | to 100 |

*Brij 92 is polyoxyethylene (2) oleyl ether

30

Example 14

This example illustrates an oil-in-water cream.

35 An oil-in-water cream emulsion having the following formulation was prepared:

- 41 -

| | | <u>% w/w</u> |
|----|---------------------------|--------------|
| | Mineral oil | 4 |
| | Sphingosine | 0.2 |
| | Phytosphingosine | 0.1 |
| 5 | Brij 56* | 4 |
| | Alfol 16RD* | 4 |
| | Triethanolamine | 0.75 |
| | Butane-1,3-diol | 3 |
| | Xanthan gum | 0.3 |
| 10 | Preservative | 0.4 |
| | Perfume | qs |
| | Butylated hydroxy toluene | 0.01 |
| | Water | to 100 |

- 15 *Brij 56 is cetyl alcohol POE (10)
 Alfol 16RD is cetyl alcohol

Example 15

- 20 This example illustrates an alcoholic lotion.

The lotion had the following formulation:

| | | <u>% w/w</u> |
|----|------------------------------|--------------|
| 25 | Tetraacetyl phytosphingosine | 0.5 |
| | Sphingosine | 0.2 |
| | Ethanol | 40 |
| | Perfume | qs |
| | Butylated hydroxy toluene | 0.01 |
| 30 | Water | to 100 |

Example 16

- 35 This example illustrates an alcoholic lotion containing a
 sphinganine derivative of the invention.

The lotion had the following formulations:

- 42 -

| | <u>% w/w</u> |
|--------------------------|--------------|
| Sphinganine derivative | |
| having the structure (3) | 0.2 |
| Dimethylsulphoxide | 10 |
| 5 Ethanol | 40 |
| Antioxidant | 0.1 |
| Perfume | qs |
| Water | to 100 |

10 Examples 17 and 18

The following compositions according to the invention represent lotions which can be used in the treatment of dry skin:

| | <u>% w/w</u> |
|--|--------------|
| 15 N-acetyl phytosphingosine (Structure 9) | 1.5 |
| Perfume | 0.1 |
| Hydroxyethyl cellulose | 0.4 |
| Absolute ethanol | 25 |
| 20 p-methyl benzoate | 0.2 |
| Sterilised demineralised water | to 100 |

CLAIMS

1. A composition suitable for topical application to human skin which comprises:

5

(i) from 0.0001 to 10% by weight of one or more ceramide pathway intermediates or precursors thereof or mixtures thereof; and

10

(ii) a balancing amount of a cosmetically acceptable vehicle for the intermediate.

2. A composition according to claim 1, in which the ceramide pathway intermediate or precursor thereof comprises sphinganine, sphingosine or phytosphingosine or a N-acyl, O-acyl or N-alkyl derivative thereof or mixture thereof.

15

3. A composition according to claim 1 or 2, in which the ceramide pathway intermediate precursor comprises N-methyl sphinganine or N,N'-dimethyl sphinganine.

20

4. A composition according to claim 1 or 2, in which the ceramide pathway intermediate precursor comprises N-methyl sphingosine or N,N'-dimethyl sphingosine.

25

5. A composition according to claim 1 or 2, in which the ceramide pathway intermediate precursor comprises N-methyl phytosphingosine or N,N'-dimethyl phytosphingosine.

30

6. A composition according to claim 1 or 2, in which the ceramide pathway intermediate comprises tetraacetyl phytosphingosine.

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7. A composition according to claim 1, in which the ceramide pathway precursor comprises serine or palmitoyl CoA.

- 44 -

8. A composition according to any preceding claim in which the ceramide pathway precursor forms from 0.01 to 5% by weight of the composition.

5 9. A composition according to any preceding claim which further comprises a ceramide pathway adjunct chosen from saturated or unsaturated alpha-, beta- or omega hydroxy fatty acids, ceramides, cholesterol, cholesterol pathway intermediates or precursors thereof, fatty acid pathway
10 intermediates or precursors thereof or mixtures thereof.

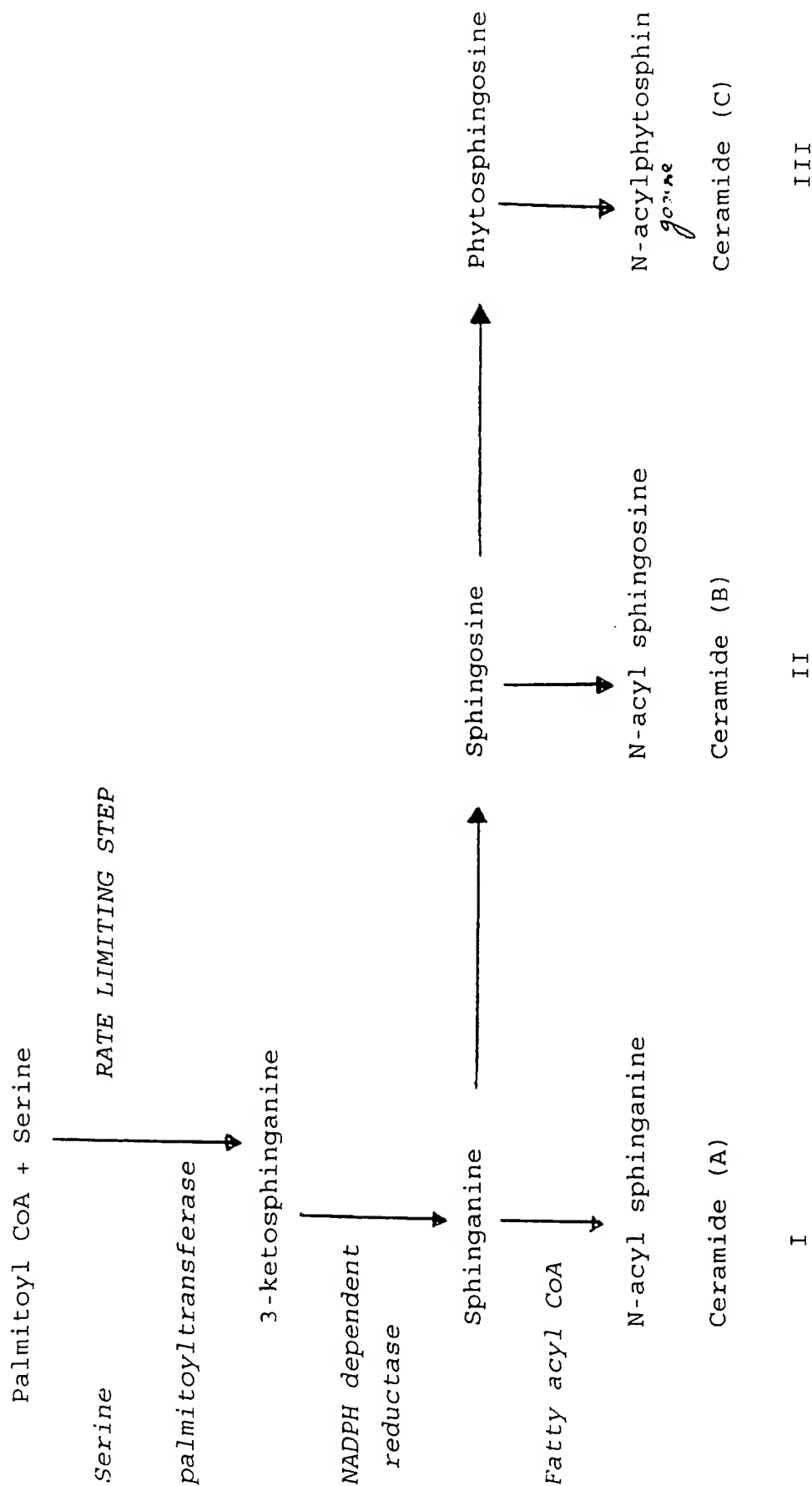
10. A method of treating skin, particularly dry or damaged skin, which comprises the step of contacting the skin topically with a ceramide pathway intermediate or a
15 precursor thereof according to claim 1.

11. The use of a ceramide pathway intermediate or a precursor thereof in accordance with claim 1, in maintaining or enhancing the skin barrier function.
20

12. The use of a ceramide pathway intermediate or a precursor thereof in the treatment of skin to reduce or delay development of wrinkling associated with advancing age, or with sun-induced skin ageing.
25

Figure 1

CERAMIDE PATHWAYS



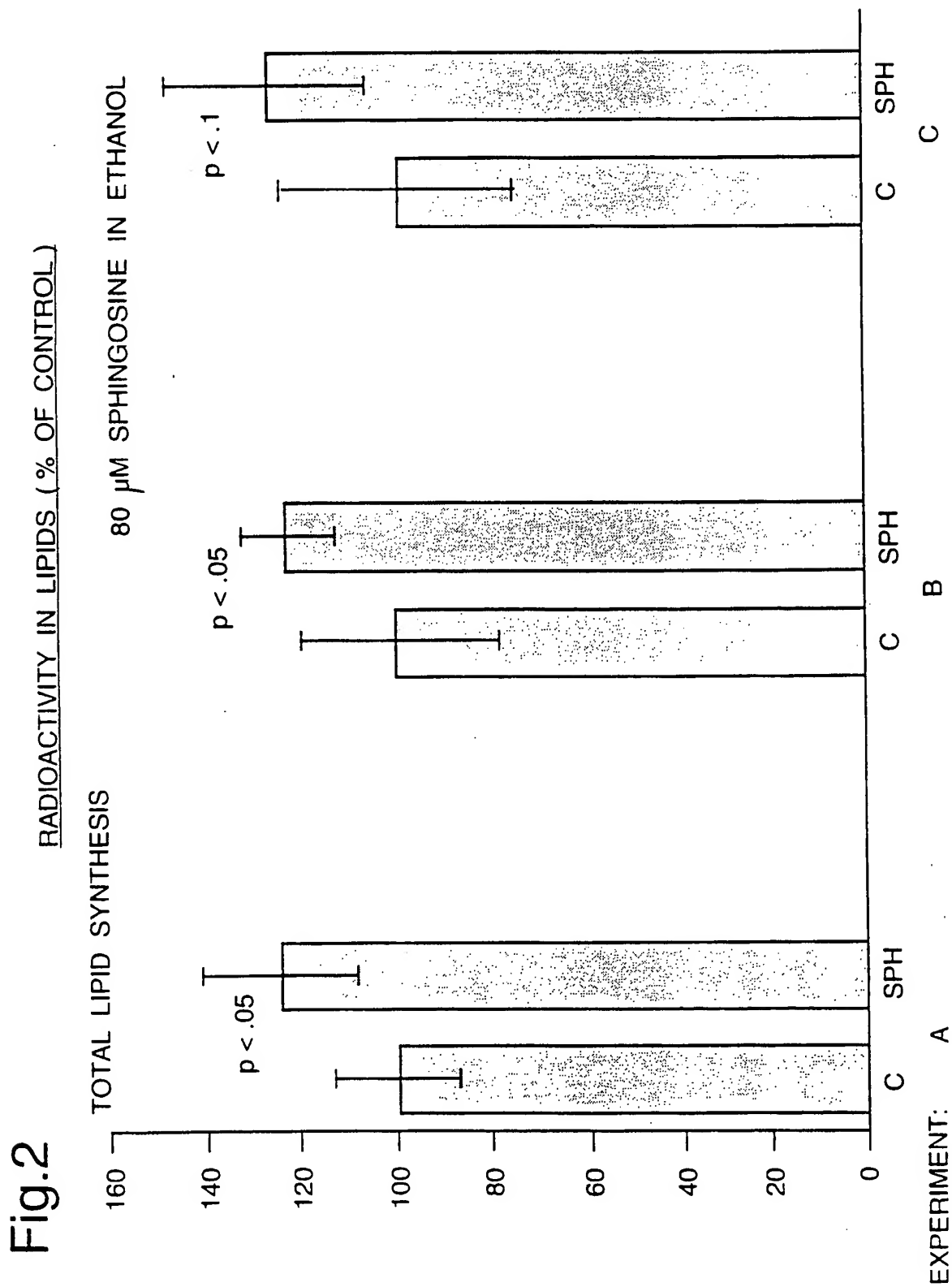
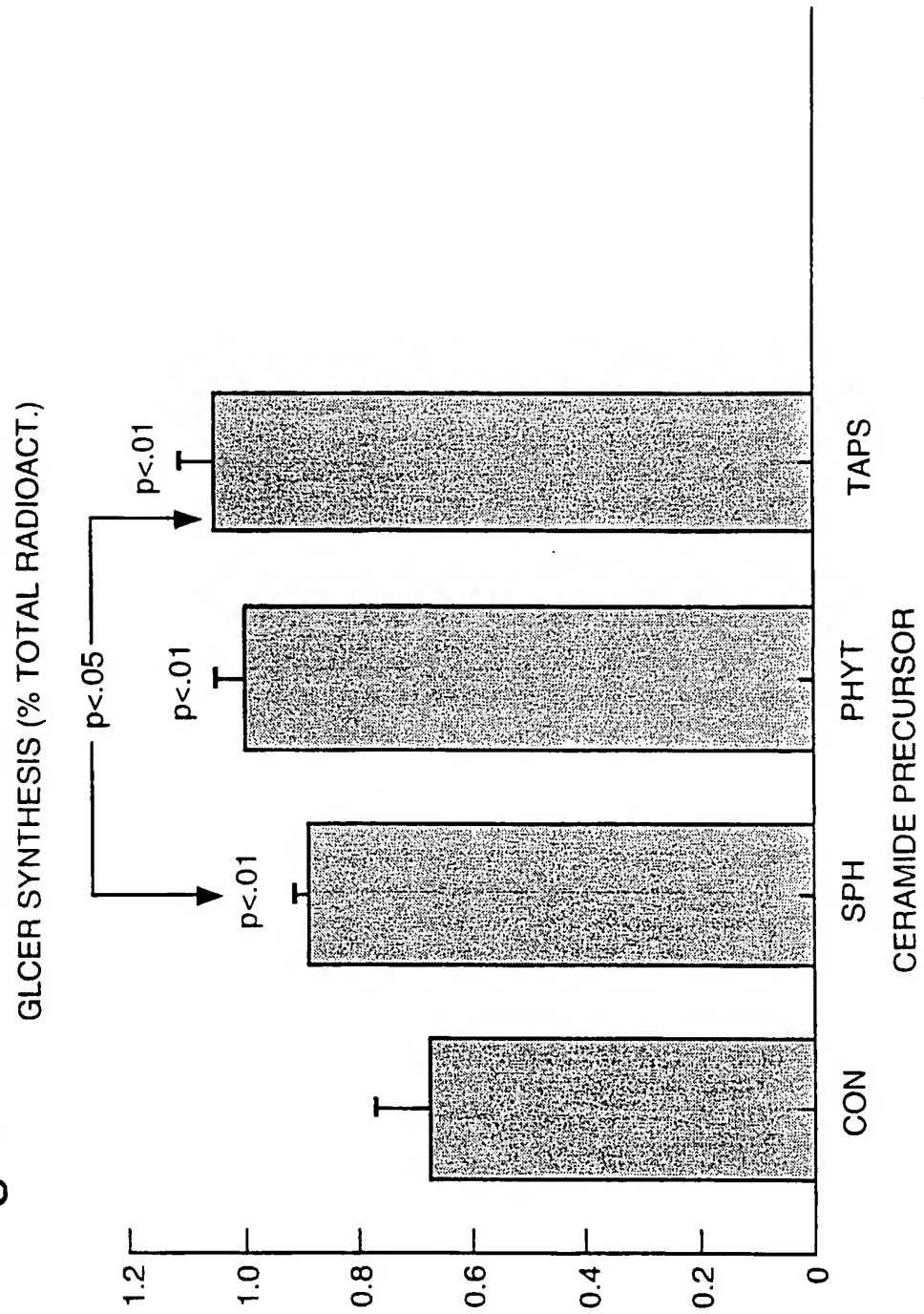


Fig.3.



A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|------------|--|-----------------------|
| X | FR,A,2 654 618 (SEDERMA) 24 May 1991 see page 3, line 4 - line 8 see page 3, line 16 - line 20 see claim 1 --- | 1,2,4,12 |
| P,X | FR,A,2 692 781 (SEDERMA) 31 December 1993 see the whole document --- | 1,8, 10-12 |
| X | WO,A,88 06034 (M.G. FIASCHETTI) 25 August 1988 see page 4 see page 5, line 1 - line 19 see page 6, line 31 - line 34 see page 7 see claims 1,6,8 ----- | 1,7, 10-12 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- "&" document member of the same patent family

Date of the actual completion of the international search

5 August 1994

Date of mailing of the international search report

16. 08 94

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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---------------------|----------------------------|---------------------|
| FR-A-2654618 | 24-05-91 | NONE | |
| FR-A-2692781 | 31-12-93 | NONE | |
| WO-A-8806034 | 25-08-88 | US-A- 4885157 | 05-12-89 |